Physical activity and left-ventricular trabeculation in the UK Biobank community-based cohort study

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ABSTRACT

Objective

Vigorous physical activity (PA) in highly trained athletes has been associated with heightened left ventricular (LV) trabeculation extent. It has therefore been hypothesised that LV trabeculation extent may participate in exercise-induced physiological cardiac remodelling. Our cross-sectional observational study aimed to ascertain whether there is a 'dose-response' relationship between PA and LV trabeculation extent, and whether this could be identified at opposite PA extremes.

Methods

In a cohort of 1,030 individuals from the community-based UK Biobank study (male/female ratio: 0.84, mean age: 61), PA was measured via total metabolic equivalent of task (MET) minutes/week and seven-day average acceleration, and trabeculation extent via maximal non-compaction/compaction ratio (NC/C) in long-axis images of cardiovascular magnetic resonance (CMR) studies. The relationship between PA and NC/C was assessed by multivariate regression (adjusting for potential confounders) as well as between demographic, anthropometric and LV phenotypic parameters and NC/C.

Results

There was no significant linear relationship between PA and NC/C (full adjustment, total MET-minutes/week: ß=-0.0008, 95%CI -0.039-0.037, p=0.97; seven-day average acceleration: ß=-0.047, 95%CI -0.110-0.115, p=0.13, per interquartile range (IQR) increment in PA), or between extreme PA quintiles (full adjustment, total MET-minutes/week: ß=-0.026, 95%CI -0.146-0.094, p=0.67; seven-day average acceleration: ß=-0.129, 95%CI -0.299-0.040, p=0.49), across all adjustment levels. A negative relationship was identified

between left-ventricular ejection fraction (LVEF) and NC/C, significantly modified by PA (ß difference=-0.006, p=0.03).

Conclusions

In a community-based general population cohort, there was no relationship at, or between, extremes, between PA and NC/C, suggesting that at typical general population PA levels, trabeculation extent is not influenced by PA changes.

Key messages:

What is already known about this subject?

It has been shown that postnatal changes which affect cardiac loading conditions affect left-ventricular (LV) trabeculation extent, such as in pregnancy and during extreme athletic-level physical activity (PA). Excessive levels of LV trabeculation form a diagnostic phenotype in left-ventricular non-compaction (LVNC) cardiomyopathy.

What does this study add?

This study provides insight into the relationship between PA and LV trabeculation extent, at levels of PA typical of a non-athletic community-based middle-aged population cohort analysed using cardiovascular magnetic resonance (CMR) imaging. We observed no relationship at or between extremes of PA within our cohort of 1,030 individuals, despite evidence to suggest exercise-induced cardiac remodelling in other parameters such as left-ventricular end-diastolic volume (LVEDV) and LV mass.

How might this impact on clinical practice?

At the PA levels typical of a community-based population, there is no evidence to suggest that excessive trabeculation, if observed, occurs as an epiphenomenon to other exercise induced cardiac remodelling processes.

INTRODUCTION

The degree of left ventricular (LV) trabeculation varies among individuals. The most documented pathological consequence of excessive trabeculation as a diagnostic phenotype is left ventricular non-compaction (LVNC), recognised as a genetic cardiomyopathy by the American Heart Association (AHA) (1), and an unclassified cardiomyopathy by both the World Health Organisation (WHO) and the European Society of Cardiology (ESC) (2,3). Prominent trabeculation is sometimes observed in the setting of dilated and hypertrophic cardiomyopathies, and in association with congenital heart defects and neuromuscular disorders (4). Therefore, it is plausible that trabeculation extent may be a morphologic expression of a wide spectrum of myocardial disease.

More recently, there is growing interest in the role of physiological influence on cardiac trabeculation. It has been shown that postnatal changes in cardiac loading conditions affect trabeculation extent using models of pregnancy and extreme physical activity (PA) (5,6). Previous literature has only identified a link between PA and trabeculation extent at the extreme level, using a cohort of highly trained athletes. To date, there has been no focussed investigation into this relationship within a community-based population cohort, with PA distribution more reflective of a general population. For this study, such a cohort was provided by the UK Biobank study - a large prospective population-based cohort study of over 500,000 participants aged 40-69 who have been recruited from 2006-2010. It aims to follow the health of these participants through comprehensive data collection at 22 centres across the UK, the core of which includes a wealth of demographic, anthropometric and environmental exposure data. A subset of these participants underwent cardiac magnetic resonance (CMR) scanning, which provided additional extensive cardiac phenotypic data (7).

Our study thus aimed to determine for the first time, in a community-based population cohort, whether the amount of PA undertaken by an individual resembled a relationship of a 'dose response' nature, as well as at high and low extremes of PA, with the degree of LV trabeculation extent observed, quantified by high-resolution (CMR) imaging.

MATERIALS AND METHODS

Participant selection

The UK Biobank has collected a wealth of phenotypic and genotypic information about its population of over 500,000 enrolled individuals, including data collection from questionnaires, physical measures, accelerometry, imaging, genome-wide genotyping with subsequent longitudinal follow-up for health-related outcomes. The sample size of 500,000 was theoretically calculated for reliable detection of the effects of different exposures on a wide variety of conditions in nested case-control studies with sufficient statistical power. The cohort's characteristics make it well-suited to study exposure-disease relationships due to its large size and heterogeneity of exposure measures. The baseline summary characteristics of the cohort can be viewed on the UK Biobank website, in the data showcase section (8). The CMR imaging sub-study of 5,065 participants occurred between 2014-2015. The study complies with the Declaration of Helsinki and was approved by our institutional review body, with all participants having provided informed written consent. The UK Biobank's scientific protocol and operational measures were approved by the Northwest Research Ethics Committee in the UK.

Classifying Physical Activity Level

For each individual, PA was measured subjectively by both total metabolic equivalent of task (MET) minutes per week using information gathered from a self-reported International Physical Activity Questionnaire (IPAQ) (9), and objectively by seven-day average acceleration in units of milli-gravity measured by a wrist-worn triaxial accelerometer. The MET is a physiological measure of energy expenditure assigned to a particular PA, which compares its relative intensity compared to rest – this was combined with the duration of PA undertaken in minutes to form the composite measure of MET-minutes. This provides a generalised measure of activity volume undertaken – for instance, 30 minutes of brisk walking per day would equal 1050 MET min/week, and jogging for the same period every day would equal 1470 MET min/week. Table 1 and both figures 1 and 2 in the supplementary material outline the calculation process.

The seven-day average acceleration measurement was acquired by an Axivity AX3 accelerometer worn continuously on the wrist of the participant's dominant hand for seven consecutive days, detecting movement in all three axes. The raw data obtained from the device captured at 100Hz was calibrated to adjust for acceleration due to local gravity using the van Hees method (10). Wear and non-wear episodes were also identified from the data (11).

CMR and trabeculation extent analysis

For all participants, all CMR studies were acquired with a wide bore 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) and the post-processing software cvi^{42} (Version 5.1.1, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used for scan analysis. LV mass, LV end-diastolic volume (LVEDV)

and LV ejection fraction (LVEF) were manually measured from balanced steady-state free precession (bSSFP) cine short and long-axis images.

These long-axis images were also used to measure trabeculation extent, using the maximal non-compaction/compaction (NC/C) ratio. There was an initial qualitative assessment for the presence of trabeculation in each of the three LV regions (basal, mid and apical) in the end-diastolic phase, defined as the visual identification of two myocardial layers represented by a difference in signal intensity between the two layers. If a trabeculated layer was visualised, the point at which the highest NC/C ratio could be obtained was measured for each region (12). The NC/C ratio was obtained by measuring the widths of the non-compacted (trabeculated) and compacted layer using the line contour tool, perpendicular to the length of the compacted layer. The highest ratio from any region of the whole scan was used to represent the trabeculation extent for that scan in the statistical analysis. Figure 1 demonstrates the process.

Statistical Analysis

All continuous variables were assessed for normality using histograms and quantile-quantile plots. Descriptive statistics for continuous variables were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), while categorical variables were presented as a frequency (percentage). Missing data, if encountered, was addressed using multiple imputation by chained equation technique to create statistically valid imputed data based on variables from the original observed dataset to form twenty differently imputed datasets. The estimates and standard errors from each imputed dataset were then pooled with Rubin's rules (13).

We constructed multiple nested linear regression models to identify any potential 'dose-response' relationship between the NC/C ratio and each PA measurement variable. We scaled both PA variables by their IQR before entering into the models to enable sensible comparison of effect estimates between the two methods of PA measurement – the effect estimates therefore indicate the change in relevant dependent variable per IQR increment in PA. In the unadjusted models, the bivariate association between PA and maximal NC/C ratio was tested. In limited models, adjustments were made for demographics and anthropometrics: age, sex, ethnicity and height. In fully-adjusted models, the remaining covariates were added – body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), smoking status, regular alcohol use, degree level education, diabetes, cardiovascular disease, hypertension, income, Townsend deprivation index, antihypertensive use, statin use, LVEDV, LV mass and LVEF.

We performed the following secondary analyses: (i) an investigation of the association between NC/C ratio and high and low PA quintiles (for each PA measurement method) using multivariate linear regression, following the same levels of adjustment, to form the extreme groups analysis, (ii) an analysis of effect modification by age, sex, BMI, LVEDV, LV mass and LVEF by introducing cross product terms to the dose-response linear regression analysis, (iii) an investigation of the fully adjusted models of multivariate regression analysis between PA and maximal NC/C ratio, to observe any significant associations between the outcome and the included covariates, (iv) an investigation of the relationship between PA and clinical cardiac parameters (LVEDV, LV mass and LVEF), to clarify whether typical physiological changes that occur in exercise-induced cardiac remodelling were exhibited in our cohort, and (v) an investigation of 'dose-response' relationships (using the same method of model construction) between PA in MET-minutes and maximal NC/C ratio at walking, moderate and vigorous PA intensities, and between categorical pre-defined PA intensity levels and

maximal NC/C ratio (of which the methodology is described in appendix 1 of the supplementary material) (14). We performed restricted cubic spline transformation of PA variables to investigate nonlinear relationships. The optimal number of knots for restricted cubic spline–transformed variables was determined by the Akaike information criterion. Twenty randomly-selected studies were independently analysed by two different readers to assess the reproducibility of NC/C ratio measurements. Inter-observer variability of repeated measurements was quantified by intra-class correlation coefficient (ICC) and was visually assessed with a Bland-Altman plot. The programming language R was used for all statistical analyses (15). p values below 0.05 were considered statistically significant. We estimated that a sample size of at least 1000 would provide 99.8% statistical power at small effect sizes (R^2 = 0.05). Table 2 in the supplementary material demonstrates the output of power calculations based on a range of R^2 values and effect sizes.

RESULTS

A total of 1,030 participants were selected randomly for analysis in this study, from the initial pool of 5,065 UK Biobank participants who had undergone CMR imaging. Figure 3 in the supplementary material summarises the selection process.

Baseline Characteristics

Table 1 shows the baseline characteristics summary for both the whole dataset, and a subset of this dataset which includes participants for which there was no missing data in all covariate fields – termed 'complete cases'. Both datasets showed a statistically significant difference – but minimal clinical difference – between the mean ages only, while means for

LVEDV, LV mass, LVEF, maximal NC/C ratio, total MET-minutes/week and overall acceleration average did not differ significantly between datasets. The original cohort was predominantly of Caucasian ethnicity, with a mean age of 61 years, where 45.7% were men.

Table 1 – Baseline characteristics for whole dataset, and complete cases (of exclusively no missing covariate data). 'Percentage complete' refers to the proportion of complete data in our whole dataset per covariate.

	Whole Dataset	**Complete Cases**	**p**	**Percentage complete (%)**
n	1030	437		
Age, years (mean [sd])	61 (7.6)	59 (6.4)	<0.001	100
Male sex (n [%])	471 (45.7)	191 (43.7)	0.513	100
Caucasian ethnicity (n [%])	1023 (99.3)	430 (98.4)	0.171	100
Height, cm (mean [sd])	169.8 (9.3)	169.8 (9.1)	0.950	100
BMI, kg/m^2 (mean [sd])	26.7 (4.2)	26.4 (4.0)	0.274	100
Weight (mean [sd])	75.5 (14.7)	74.8 (14.3)	0.386	100
Systolic blood pressure, mmHg (mean [sd])	136.4 (18.0)	135.2 (17.7)	0.250	99.9
Diastolic blood pressure, mmHg (mean [sd])	78.7 (9.7)	78.7 (9.3)	0.990	99.9
Heart rate, bpm (mean [sd])	70 (11.8)	70 (11.4)	0.902	100
Average household income before tax (n [%])			0.726	89.3
Less than £18,000	129 (14.0)	56 (12.8)		
£18,000 to £30,999	270 (29.3)	117 (26.8)		
£31,000 to £51,999	285 (31.0)	139 (31.8)		
£52,000 to £100,000	180 (19.6)	96 (22.0)		
Greater than £100,000	56 (6.1)	29 (6.6)		
Degree level or professional education (n [%])	652 (63.3)	290 (66.4)	0.290	100
Townsend deprivation index (mean [sd])	-1.87 (2.68)	-1.76 (2.60)	0.472	100
Smoking status (n [%])			0.731	98.4
Never	611 (60.3)	255 (58.4)		
Previous	361 (35.6)	161 (36.8)		
Current	42 (4.1)	21 (4.8)		
Regular alcohol use (n [%])	446 (43.8)	189 (43.2)	0.888	98.8
Diabetes mellitus (n [%])	56 (5.4)	23 (5.3)	0.993	100
Cardiovascular disease (n [%])	91 (8.8)	24 (5.5)	0.038	100
Hypertension (n [%])	322 (31.3)	135 (30.9)	0.938	100
Antihypertensive use, (n [%])	237 (23.0)	97 (22.2)	0.786	100
Statin use (n [%])	225 (21.8)	77 (17.6)	0.078	100
LVEDV, ml/m^2 (mean [sd])	145.2 (33.4)	145.9 (33.0)	0.707	98.2
LV mass, g/m^2 (mean [sd])	89.2 (24.1)	88.5 (23.4)	0.595	98.2
LVEF, % (mean [sd])	59.4 (5.9)	59.5 (5.6)	0.968	98.2
Maximal NC/C Ratio (mean [sd])	1.93 (0.50)	1.91 (0.51)	0.508	100

Total MET-minutes/week, MET-min/week (median [IQR])	2115 (3599)	2226 (4061)	0.214	73.1
Seven-day average acceleration, milli-gravity (median [IQR])	27.56 (13.50)	28.41 (14.40)	0.164	62.6

Splitting the range of values for both PA measurement methods produced the following quintiles: for total MET-minutes per week these were 0-794.4, 794.4-1626, 1626-2853, 2853-5193, and 5193 to 24318 MET-min/week, and for average acceleration these were 0.05-20.7, 20.7-25.7, 25.7-30.6, 30.6-37.6, and 37.6-67.1 units of milli-gravity. Figure 4 in the supplementary material demonstrates the similar distribution of PA in total MET-minutes per week across the cohort, relative to the original CMR pilot study cohort of 5065 individuals. Maximal NC/C values ranged from 0.71 to 3.67, with a median of 2.00. There was a high level of agreement between repeated measurements of NC/C values as indicated by ICC (0.75) and the Bland-Altman plot in figure 5 of the supplementary material.

'Dose-response' and extreme groups relationship analysis

Pooled multivariate regression was carried out between total MET and seven-day average acceleration, and maximal NC/C ratio, after multiple imputation. For both methods of PA measurement, there was no significant linear relationship demonstrated between PA and maximal NC/C ratio at all adjustment levels. Additionally, restricted cubic spline analyses showed no convincing evidence to support nonlinear relationships (Figure 6 in the supplementary material).

Pooled multivariate regression was also performed between the lowest and highest PA quintiles of the cohort and maximal NC/C ratio for both PA measurement methods after multiple imputation. At all levels of model adjustment for both methods of PA measurement, no significant relationship was found between PA and maximal NC/C ratio between lowest

and highest quintiles of PA values. Table 2 shows the analysis of both the dose-response and the extreme groups relationship.

Table 2 – Association between PA (measured in both total MET-minutes/week and overall seven day average acceleration) and maximal NC/C ratio, for both the dose-response and extreme groups analysis. Effect estimate reflects an NC/C ratio change per IQR of either total MET-minutes/week or seven-day average acceleration.

		Model								
		Unadjusted			Limited adjustment			Full adjustment		
Clinical Cardiac Parameter	PA Measurement Method	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value
Dose-response analysis	Total MET-minutes/week	0.019	-0.019 to 0.056	0.32	0.024	-0.013 to 0.060	0.20	-0.001	-0.039 to 0.037	0.97
	Seven-day average acceleration	-0.012	-0.062 to 0.039	0.65	-0.007	-0.059 to 0.045	0.79	-0.047	-0.110 to 0.015	0.13
Extreme groups analysis	Total MET-minutes/week	0.049	-0.060 to 0.158	0.38	0.062	-0.046 to 0.171	0.26	-0.026	-0.146 to 0.094	0.67
	Seven-day average acceleration	-0.036	-0.157 to 0.086	0.56	-0.017	-0.144 to 0.111	0.79	-0.129	-0.299 to 0.040	0.49

Effect modification by cross-products

In fully adjusted models, age, sex, BMI, LVEDV and LV mass all produced no significant effect modifications on the continuous relationship between PA (in both measurement methods) and maximal NC/C ratio. LVEF was the only covariate to produce a significant effect modification when PA was measured in total MET-minutes/week. There was an overall negative relationship between LVEF and NC/C ratio, where one SD increment in LVEF was associated with a decrease of 0.04 units of maximal NC/C ratio. Incorporating PA (when measured in total MET-minutes/week) with LVEF as a crossproduct significantly modified this relationship by augmenting the negative relationship between LVEF and NC/C ratio ($p = 0.03$).

Association between covariates and NC/C ratio in the fully adjusted models

Tables 3 and 4 show the results of the fully adjusted multivariate regression models carried out between both methods of PA measurement and maximal NC/C ratio, in our 'dose-response' analysis. Both models showed positive associations between female sex and LVEDV and maximal NC/C ratio, as well as negative associations between LV mass and LVEF and maximal NC/C ratio. The model investigating PA in total MET-minutes/week showed a positive association between age and NC/C ratio. The model investigating PA in overall seven-day average acceleration showed a negative association between BMI and maximal NC/C ratio.

Table 3: Fully adjusted multivariate regression model from analysis of the relationship between PA in total MET-minutes per week and maximal NC/C ratio (p values less than 0.05 are in bold).

Covariate	Effect estimate	Standard error	95% confidence interval		p
			Low	High	
Age (per SD: 7.68 years)	0.041	0.015	0.000	0.077	**0.031**
Sex (Male)	-0.169	0.050	-0.267	-0.071	**0.001**
Ethnicity (Caucasian)	0.210	0.182	-0.148	0.568	0.249
Height (per SD: 9.26cm)	-0.009	0.028	-0.065	0.037	0.610
BMI (per SD: 4.19kg/m2)	-0.034	0.017	-0.071	0.000	0.054
SBP (per SD: 18.0mmHg)	-0.018	0.018	-0.072	0.018	0.344
DBP (per SD: 9.64mmHg)	-0.010	0.019	-0.058	0.029	0.640
HR (per SD: 11.7bpm)	0.012	0.012	-0.023	0.047	0.476
Average household income before tax:					
Less than £18,000	0.014	0.053	-0.089	0.117	0.788
£31,000 to £51,999	-0.053	0.041	-0.134	0.027	0.192
£52,000 to £100,000	-0.067	0.049	-0.163	0.029	0.170
Greater than £100,000	-0.005	0.073	-0.147	0.138	0.946
Degree level or professional education	-0.041	0.032	-0.105	0.022	0.204
Townsend deprivation index (per SD: 2.68)	-0.021	0.016	-0.054	0.011	0.178

Smoking status:					
Never smoked	-0.028	0.078	-0.181	0.125	0.718
Previous smoker	-0.052	0.079	-0.208	0.103	0.509
Regular alcohol use	-0.021	0.032	-0.083	0.042	0.519
Diabetes mellitus	-0.082	0.070	-0.220	0.055	0.240
Cardiovascular disease	-0.014	0.058	-0.127	0.100	0.811
Hypertension	-0.084	0.057	-0.196	0.027	0.138
Antihypertensive use	0.017	0.064	-0.108	0.142	0.790
Statin use	0.002	0.044	-0.084	0.089	0.956
LVEDV (per SD: 33.3ml/m2)	0.166	0.025	0.112	0.210	**< 0.001**
LV mass (per SD: 24.1g/m2)	-0.120	0.028	-0.174	-0.065	**< 0.001**
LVEF (per SD: 5.91%)	-0.033	0.016	-0.064	-0.016	**0.039**
Total MET-minutes per week (per IQR: 3505 MET-min/week)	-0.001	0.019	-0.039	0.037	0.966

Table 4: Fully adjusted multivariate regression model from analysis of the relationship between PA in average acceleration and maximal NC/C ratio (p values less than 0.05 are in bold).

Covariate	Effect estimate	Standard error	95% confidence interval		p
			Low	High	
Age (per SD: 7.68 years)	0.030	0.023	0.000	0.068	0.077
Sex (Male)	-0.175	0.050	-0.273	-0.077	**< 0.001**
Ethnicity (Caucasian)	0.167	0.184	-0.194	0.528	0.365
Height (per SD: 9.26cm)	-0.019	0.028	-0.065	0.028	0.416
BMI (per SD: 4.19kg/m2)	-0.046	0.021	-0.088	-0.008	**0.014**
SBP (per SD: 18.0mmHg)	-0.018	0.018	-0.072	0.018	0.366
DBP (per SD: 9.64mmHg)	-0.010	0.019	-0.058	0.029	0.622
HR (per SD: 11.7bpm)	0.012	0.012	-0.023	0.047	0.638
Average household income before tax:					
Less than £18,000	0.017	0.053	-0.088	0.122	0.751
£31,000 to £51,999	-0.052	0.041	-0.132	0.029	0.210
£52,000 to £100,000	-0.069	0.049	-0.164	0.027	0.158
Greater than £100,000	-0.014	0.073	-0.157	0.129	0.845
Degree level or professional education	-0.036	0.032	-0.100	0.027	0.263
Townsend deprivation index (per SD: 2.68)	-0.021	0.016	-0.054	0.011	0.174
Smoking status:					
Never smoked	-0.019	0.078	-0.172	0.134	0.807
Previous smoker	-0.042	0.080	-0.198	0.114	0.600

Regular alcohol use	-0.020	0.032	-0.082	0.043	0.536
Diabetes mellitus	-0.083	0.070	-0.220	0.054	0.235
Cardiovascular disease	-0.022	0.058	-0.136	0.091	0.698
Hypertension	-0.091	0.057	-0.202	0.021	0.110
Antihypertensive use	0.019	0.063	-0.105	0.144	0.761
Statin use	0.002	0.044	-0.084	0.088	0.962
LVEDV (per SD: 33.3ml/m2)	0.165	0.025	0.116	0.214	**< 0.001**
LV mass (per SD: 24.1g/m2)	-0.110	0.028	-0.165	-0.055	**< 0.001**
LVEF (per SD: 5.91%)	-0.034	0.016	-0.065	-0.003	**0.034**
Seven-day average acceleration (per IQR: 13.4 milli-gravity)	-0.047	0.031	-0.110	0.015	0.133

Relationship between PA and clinical cardiac parameters

Across all levels of adjustment, there was no significant relationship between PA and LVEF with both methods of PA measurement. However, with full adjustment, there was a significant positive relationship between PA (in both measurement methods) and LV mass, with a similar significant relationship also observed at limited adjustment when PA was measured in seven-day average acceleration. The analysis of these relationships is shown in Table 5. In addition, there was a significant positive relationship between PA (in both measurement methods) and LVEDV across all adjustments (Full adjustment in total MET-minutes/week: ß = 1.509 per 1 IQR increment, 95% CI 0.028 to 2.990, p = 0.046; Full adjustment in seven-day average acceleration: ß = 2.474 per 1 IQR increment, 95% CI 0.053 to 4.895, p = 0.045).

Table 5 – Associations between PA (in both methods of measurement) and LVEF, and PA and LV mass. Effect estimate reflects an LVEF (in %) or LV mass (in g/m^2) change per IQR of either total MET-minutes/week or seven-day average acceleration.

	Model		
	Unadjusted	Limited adjustment	Full adjustment

Clinical Cardiac Parameter	PA Measurement Method	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value
LVEF	Total MET-minutes/week	-0.440	-0.886 to 0.006	0.053	-0.415	-0.863 to 0.032	0.069	-0.233	-0.687 to 0.221	0.312
	Seven-day average acceleration	-0.501	-1.044 to 0.041	0.070	-0.514	-1.079 to 0.050	0.073	-0.231	-0.895 to 0.433	0.493
LV mass	Total MET-minutes/week	1.388	-0.222 to 2.998	0.091	0.969	-0.178 to 2.115	0.097	1.344	0.380 to 2.307	0.006
	Seven-day average acceleration	2.329	-0.153 to 4.811	0.066	2.587	-0.767 to 4.407	0.005	3.480	1.839 to 5.121	<0.001

Dose response and categorical intensity analysis between PA and maximal NC/C ratio

Table 6 shows the pooled multivariate regression analysis, after multiple imputation, between PA in MET-minutes per week at walking, moderate and vigorous PA intensities and maximal NC/C ratio, as well as between PA at categorical low vs. moderate, and categorical low vs. high PA intensity, and maximal NC/C ratio. At all levels of adjustment, no significant relationship was found.

Table 6 – Association between PA (measured in i) walking, moderate, and vigorous MET-minutes/week, and ii) low vs. moderate and high PA intensity) and maximal NC/C ratio. Effect estimate reflects an NC/C ratio change per IQR MET-minutes/week.

	Model								
	Unadjusted			Limited adjustment			Full adjustment		
PA Measurement Method	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value	Effect Estimate	95% CI	*p* value
Total walking MET-minutes/week	0.006	-0.024 to 0.037	0.68	0.005	-0.025 to 0.035	0.76	-0.007	-0.037 to 0.023	0.65
Total moderate MET-minutes/week	0.001	-0.033 to 0.035	0.95	0.002	-0.031 to 0.036	0.88	-0.018	-0.052 to 0.016	0.31

Total vigorous MET-minutes/week	0.016	-0.007 to 0.039	0.19	0.021	-0.001 to 0.044	0.06	0.006	-0.017 to 0.029	0.60
Low vs. moderate categorical activity	0.045	-0.039 to 0.130	0.29	0.048	-0.035 to 0.131	0.26	0.022	-0.060 to 0.104	0.60
Low vs. high categorical activity	0.009	-0.073 to 0.092	0.83	0.022	-0.058 to 0.104	0.58	-0.037	-0.119 to 0.046	0.39

DISCUSSION

In our study, the first to examine the relationship between PA and LV trabeculation extent in a community-based cohort using CMR imaging, the following observations were made. Firstly, there was no linear relationship between PA and maximal NC/C ratio, for both PA measurement methods. Secondly, there was no significant difference in maximal NC/C ratio between the lowest and highest PA extreme groups for both PA measurement methods. Thirdly, PA (measured in total MET-minutes/week) augmented the negative relationship between LVEF and maximal NC/C ratio. Finally, age and LVEDV exhibited a significantly positive linear relationship with maximal NC/C ratio, whilst male sex, BMI, LV mass and LVEF exhibited a significantly negative linear relationship with maximal NC/C ratio.

Studies that previously hypothesised that LV trabeculation extent may participate in the exercise-induced cardiac remodelling process using models of pregnancy and extreme athletically trained PA levels found increased trabeculation extent in tandem with other phenotypical LV changes expected under these preload increasing conditions, such as increased LV mass, LVEDV and LV cavity size (5,6). No linear relationship was identified between PA and LV trabeculation extent, despite evidence to suggest exercise induced cardiac remodelling, namely a significant positive linear relationship between PA and LVEDV, and PA and LV mass. This suggests that within a community-based population,

trabeculation extent is not a cardiac phenotype that is significantly sensitive enough to be influenced by PA, reinforced by the lack of a significant 'dose-response' relationship found between PA in MET-minutes/week and maximal NC/C ratio at vigorous PA intensity levels. In addition, there was no significant effect of extreme PA on trabeculation extent in our extreme groups analysis. This finding contrasts with the results of Gati's study in 2013 of a similar sample size, where athletes displayed a higher prevalence of increased LV trabeculation (18.3%) compared with controls (7.0%) (6).

It could therefore be suggested that there exists a PA threshold which must be exceeded for increased trabeculation extent to manifest as a phenotypical change in response to increased PA. As Gati's study selected athletes 'competing at regional or national levels' that were aged between 14 and 35, it was more likely to select for elite athletes compared to that of our cohort, with an older age range and more reflective of a general community-based population. It is therefore possible that the PA levels reached by the cohort in our study were not high enough to produce trabeculation changes of sufficient magnitude to be detected despite our large sample size.

Effect size modification by covariates was also investigated. In the fully adjusted model, including LVEF as a cross product produced a significant effect size modification in the relationship between PA (in total MET-minutes/week) and maximal NC/C ratio. Given the significant negative relationship found in our study between LVEF and maximal NC/C ratio, the effect modification analysis suggests that PA may have some degree of further negative influence on this relationship.

Our study also echoed previous research within another community based cohort – the Multi-Ethnic Study of Atherosclerosis (MESA), where higher PA levels resulted in both an

increased LVEDV and a decreased resting HR (16). Further research performed using the MESA cohort also identified influencing factors on trabeculation extent similar to our study, where both female sex and higher LVEDV were associated with a higher maximal NC/C ratio. However, this study identified no association between LVEF and maximal NC/C ratio, which contrasts with our study's findings (17).

Evidence from another recent study has further validated our finding of an association between LVEDV and trabeculation extent. This was undertaken in a healthy Singaporean Chinese cohort, which found LVEDV to also be positively concordant with LV trabeculation extent, measured by fractal dimension (FD) analysis (18). This study also reported a positive association between LV mass and LV trabeculation extent, whereas in contrast our study found a negative association between LV mass and maximal NC/C ratio. This can however be explained by hearts with higher LV mass exhibiting a thicker compacted myocardium, thereby reducing maximal NC/C ratio values in our study by augmenting the denominator.

Limitations

There were some limitations of the data relevant to our study. The total MET-minutes/week measurement of PA was self-reported, reducing the consistency of recordings due to differing interpretations of the questionnaire by each participant. The calculation process in the questionnaire also did not take into account more precise measures of the amount of each exact type of PA undertaken, instead grouping activities into three relative MET intensities for calculation. Seven-day average acceleration was a more objective alternate measurement gained from the wrist-worn accelerometer, but the one-week sample period may not have produced average estimates as accurate as those from a longer sample period. Also, the values produced by average measurements may not have been large enough to reflect a potential 'threshold dose' of PA, above which an effect on maximal NC/C ratio may have

been observed.

Our study was also limited in the trabeculation measurement method used. As the maximal NC/C ratio was taken for the LV globally, regional distribution of LV trabeculation was therefore not considered, meaning that more detailed region-specific analysis could not be performed, such as the impact of PA purely on apical trabeculation extent. Also, much previous analysis of LV trabeculation has been performed using echocardiographic data (5,6), which is the most common method of assessing LV trabeculation extent in the context of clinically diagnosing LVNC (19). Such data is unavailable from the UK Biobank, which limits potential parallel analyses comparing echocardiographic and CMR data for each participant. The accuracy of estimates generated using multiple imputation to account for missing data is most optimal if the missing values are 'missing at random', hence depend on observed existing data rather than unobserved external factors. Additionally, as our study was cross-sectional, relevant time periods for physiological cardiac remodelling were not defined, therefore concrete inferences about whether a causal link exists between PA levels and trabeculation extent should be interpreted with caution in the absence of longitudinal data.

Future direction

While our study used well known measures of both trabeculation and PA, it would be valuable to additionally explore this relationship using different approaches to these measurements.

Increasing the time over which the average acceleration is measured would increase its validity by accounting further for the variation that exists between individuals' activity patterns. In addition, using the accelerometer to gain a measurement of direct activity

intensity may better differentiate those that indeed undergo the most athletic activity in the cohort, which would introduce a more robust analysis of the relationship at low and high PA extremes.

Trabeculation extent could alternatively be measured by FD. This is a more automated measurement than the NC/C ratio, which is based on the fractal biology in which trabeculation is structured to measure the complexity of the trabeculation in short-axis CMR slices. Whilst removing the possibility of analysis of compacted myocardial thickness (due to no involvement of compacted wall measurement), FD takes trabeculation measurement into account across the whole LV, allowing for region-specific analysis as well as demonstrating marginally higher intra-observer reproducibility than NC/C ratio measurements (20).

Conclusions

In the first study to investigate the relationship between PA and LV trabeculation extent within a community-based sample population using CMR imaging, our results showed no significant relationship between PA and maximal NC/C ratio, in a cohort that demonstrated characteristics of exercise-induced cardiac remodelling. At the levels of activity recorded, there was no evidence to suggest that trabeculation changes occur as an epiphenomenon to other processes in this remodelling. The possibility of whether exercise-related changes in trabeculation extent occur above a certain threshold of PA, and where this threshold lies, remains to be investigated.

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DISCLOSURES

SEP provides consultancy to Circle Cardiovascular Imaging Inc, Calgary, Canada. Other authors have no conflicts of interest to declare.

CONTRIBUTORSHIP STATEMENT

SPW and NA designed the study and performed statistical analysis, with data acquired by NA and SEP and trabeculation measurements performed by SPW. SPW wrote the first draft of the manuscript, with critical review from NA and SEP. All authors contributed to data interpretation and draft revision until approval of the final version.

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Figure 1 Legend:

A demonstration of the measurement of the widths of the non-compacted and compacted layers using the cvi[42] software. Measurements are indicated by the yellow lines. Measurements were labelled in the format '(region)_(compaction level)' – for example 'apex_NC' indicates a non-compacted layer in the apex. (a), (b) and (c) indicate the 4, 3 and 2 chamber long-axis views respectively, and (d) indicates the short axis view for reference. The widths of each measurement are displayed at the bottom-centre of each long axis view. These were used to calculate the NC/C ratio.

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Supplementary Material

Table 1 – Example MET values assigned to various forms of PA, grouped into light, moderate, and vigorous PA levels (11). The MET is a physiological measure of energy expenditure assigned to a particular PA. Since one MET is defined as the energy spent while an individual is at rest, MET is a measure of the intensity of the activity compared to rest. For instance, a MET value of 7 applied to the activity would mean that the activity expends 7 times the amount of energy (typically the amount of calories) compared to rest.

Light activity (<3.0 METs)	**Moderate Activity (3.0 – 6.0 METs)**	**Vigorous Activity (>6.0 METs)**
Walking – slowly = 2.0	Walking – very brisk = 5.0	Walking/hiking (4-5mph) = 7.0 Jogging at 6mph = 10.0
Sitting – using computer = 1.5	Cleaning – heavy = 3.0-3.5 (washing windows, vacuuming, mopping)	Shovelling = 7.0-8.5
Standing – light work = 2.0-2.5 (cooking, washing dishes)	Mowing lawn = 5.5 (walk power mower)	Carrying heavy loads = 7.5
Fishing – sitting = 2.0 Playing most instruments = 2.0-2.5	Bicycling – light effort (10-12mph) = 6.0 Badminton – recreational = 4.5 Tennis – doubles = 5.0	Bicycling fast (14-16mph) = 10.0 Basketball game = 8.0 Soccer casual = 7.0 Tennis – singles = 8.0

(1) In a typical **week**, on how many **days** did you walk for at least 10 minutes at a time? (Includes walking that you do at work, travelling to and from work, and for sport or leisure)
(2) How many **minutes** did you usually spend walking on a typical **day**?
(3) In a typical **week**, on how many **days** did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace?
(4) How many **minutes** did you usually spend doing moderate activities on a typical **day**?
(5) In a typical **week**, how many **days** did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)
(6) How many **minutes** did you usually spend doing vigorous activities on a typical **day**?

Figure 1 - Example questions for participants in the self-reported IPAQ questionnaire.

Walking MET-minutes/week = 3.3 x walking days (1) x walking minutes (2)

Moderate MET-minutes/week = 4.0 x moderate-intensity days (3) x moderate-intensity activity minutes (4)

Vigorous MET-minutes/week = 8.0 x vigorous-intensity days (5) x vigorous-intensity activity minutes (6)

Total MET minutes per week = Walking + Moderate + Vigorous MET-min/week scores

Figure 2 - Calculations culminating in the total MET minutes per week, using information gained from the IPAQ questions in figure 1 (Craig et al., 2003).

Table 2 – Power calculations based on potential sample sizes against a range of R^2 values, with a p value less than 0.05 indicating statistical significance.

		Sample size		
		250	500	1000
R^2	0.05	45.6%	85.9%	99.8%
	0.10	86.5%	99.9%	100%
	0.15	98.6%	99.9%	100%
	0.20	99.9%	100%	100%

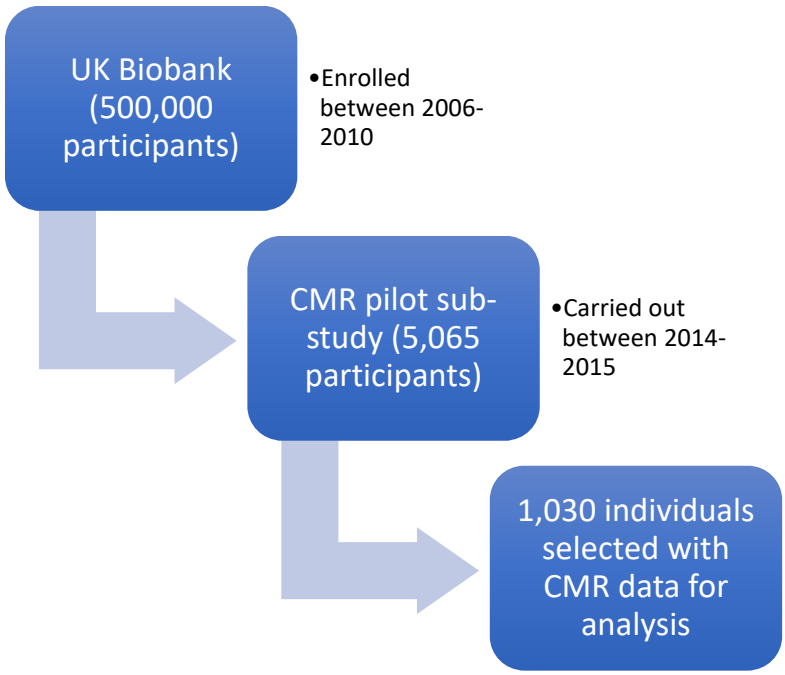

Figure 3 – A flowchart summarising the selection process for the individuals investigated in this study.

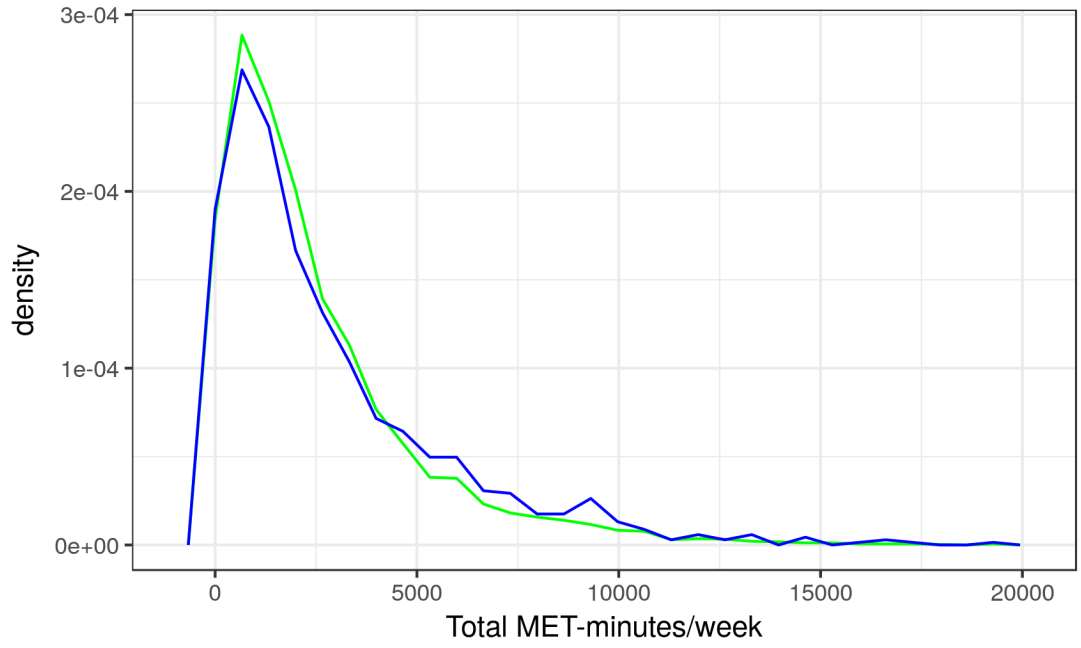

Figure 4 – A density plot demonstrating the distribution of PA in total MET-minutes per week across the study cohort of 1030 individuals (blue) relative to that of the original CMR pilot study of 5065 individuals (green)

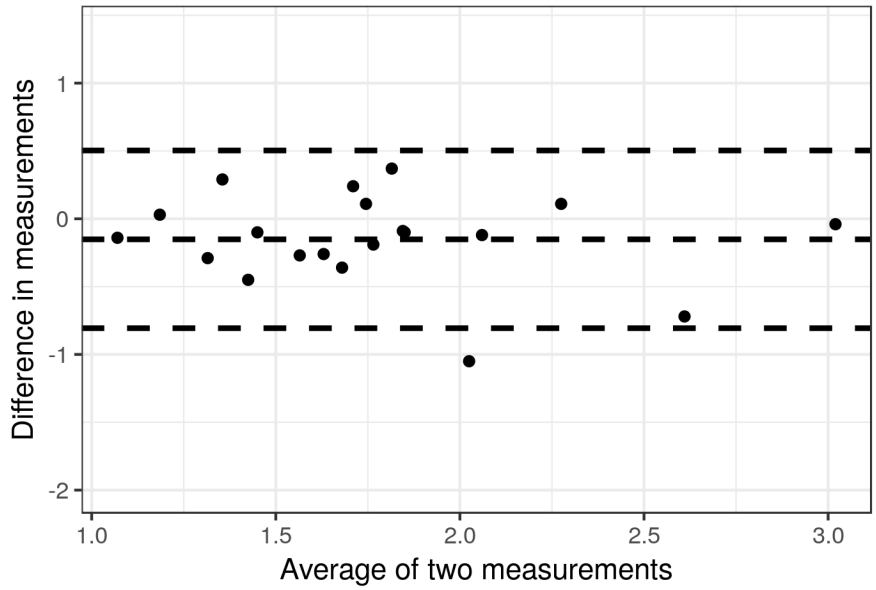

Figure 5 – A Bland-Altman plot demonstrating the inter-observer variability of NC/C ratio values in 20 studies

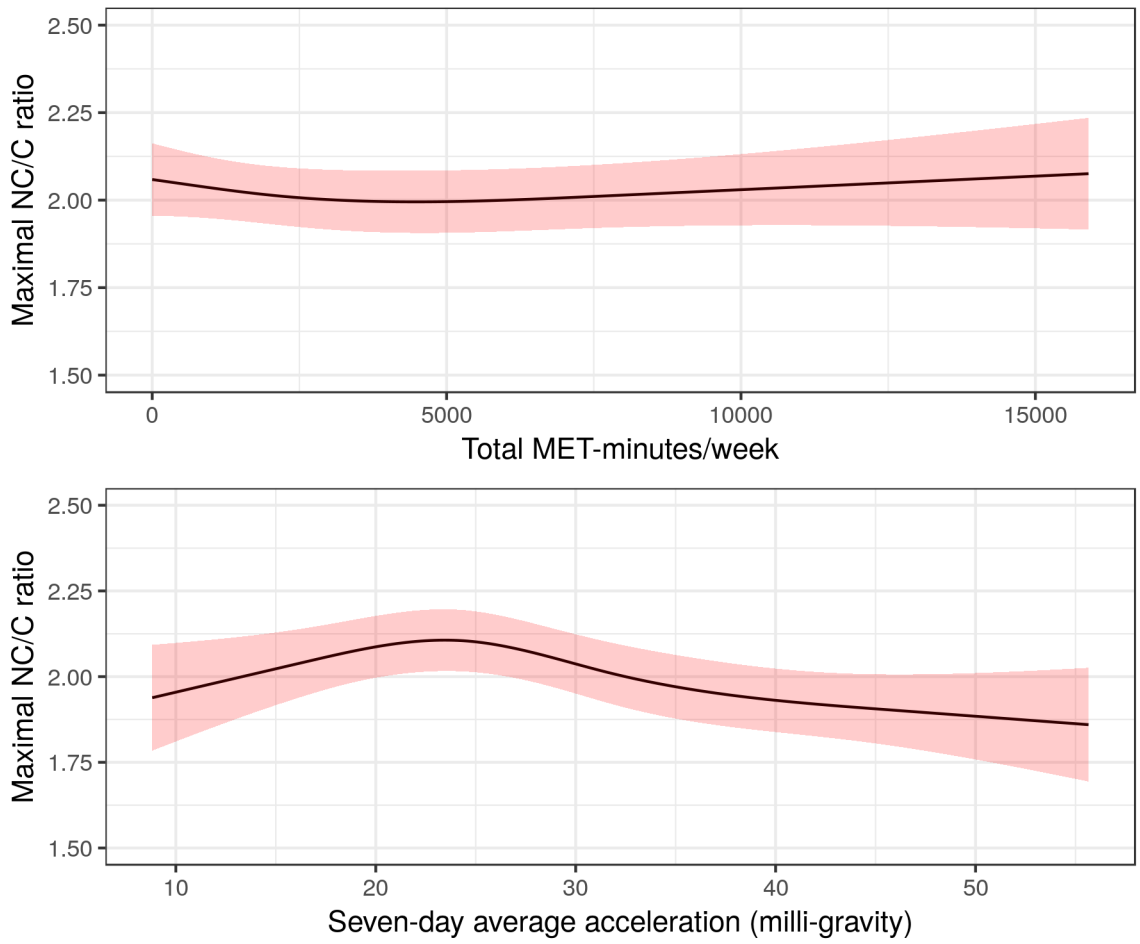

Figure 6 – Association between restricted-cubic-spline-transformed PA measurements and maximal NC/C ratio. The line and the shaded area represent the predicted mean and 95% confidence interval of maximal NC/C ratio. The plots did not demonstrate a clear evidence of non-linear relationship.

Appendix 1:

Methodology of PA intensity category definition

In addition to our other methods of PA measurement, the cohort was split categorically into low, moderate, and high PA intensity levels using criteria as per official IPAQ recommendations and guidance. Moderate PA comprised either a) Over or equal to 3 days of vigorous intensity PA of at least 20 minutes/day OR b) Over or equal to 5 days of moderate-intensity PA and/or walking of at least 30 minutes/day OR c) Over or equal to 5 days of any combination of walking, moderate or vigorous-intensity PA achieving a minimum of at least 600 MET-minutes/week. High PA comprised either a) vigorous intensity PA on at least 3

days achieving a minimum total PA of 1500 MET-minutes/week OR b) Over or equal to 7 days of any combination of walking, moderate or vigorous-intensity PA achieving a minimum total PA of 3000 MET-minutes/week. Low PA was defined in those individuals not meeting criteria for moderate or high PA.